Biochemistry of Endocrine System

The nervous and endocrine systems are the two major regulatory systems of the body, and together they regulate and coordinate the activity of essentially all other body structures. The **endocrine system** is composed of glands that secrete chemical signals into the circulatory system. In contrast, **exocrine glands** have ducts that carry their secretions to surfaces. The secretary products of endocrine glands are called hormones.

Traditionally, a **hormone** is defined as a chemical signal, or ligand that synthesized in one organ and transported by the circulatory system to act on another tissue. However, this original description is too restrictive because hormones can act on adjacent cells (paracrine action) and on the cell in which they were synthesized (autocrine action) without entering the systemic circulation, as explained in Figure (1):

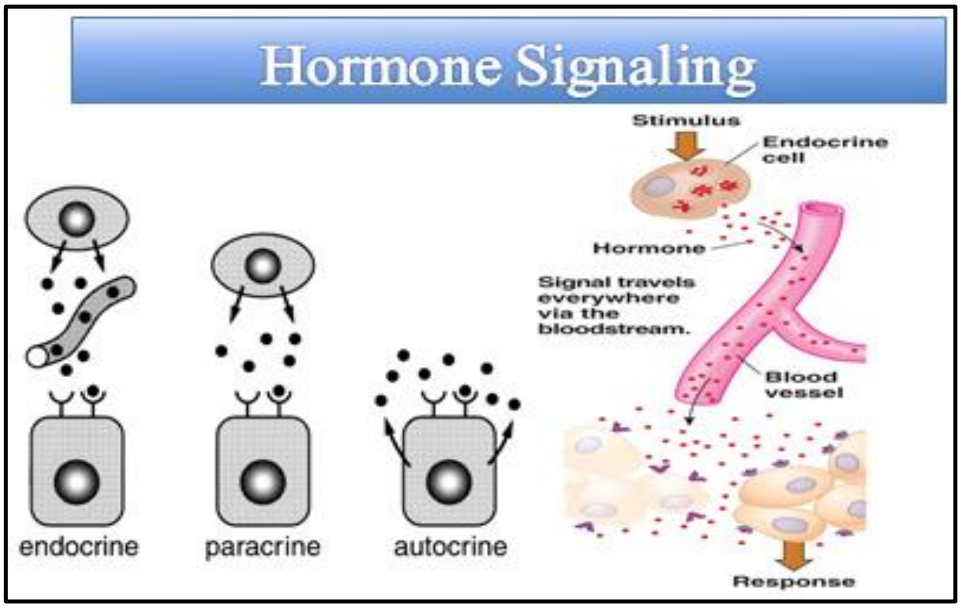

Figure (1) Hormone signaling

Target cell

The definition of a target includes any cell in which the hormone (ligand) binds to its receptor, whether or not a biochemical or physiologic response has yet been determined. The hormone can affect several different cell types; also more than one hormone can affect

a given cell type; and that hormones can exert many different effects in one cell or in different cells.

Hormone receptors

Target cells must distinguish not only between different hormones present in small amounts but also between a given hormone and other similar molecules. This high degree of discrimination is provided by cell associated recognition molecules called **receptors**. Hormones initiate their biologic effects by binding to specific receptors, and terminate its actions when the effecter dissociates from the receptor. Several biochemical features of this interaction are important in order for hormone receptor interactions to be physiologically relevant:

(1) Binding should be specific.
(2) Binding should be saturable.
(3) Binding should occur within the concentration range of the expected biologic response.

All receptors have at least two functional domains. The first, recognition domain binds the hormone ligand and a second region generates a signal that couples hormone recognition to some intracellular function. Coupling domain (signal transduction) occurs in two general ways. Polypeptide and protein hormones and the catecholamines bind to receptors located in the plasma membrane and thereby generate a signal that regulates various intracellular functions, often by changing the activity of an enzyme. In contrast, steroid, retinoid, and thyroid hormones interact with intracellular receptors, and it is this ligand receptor complex that directly provides the signal, generally to specific genes whose rate of transcription is thereby affected.

The cell surface receptor and intracellular receptor are appeared in Figure (2):

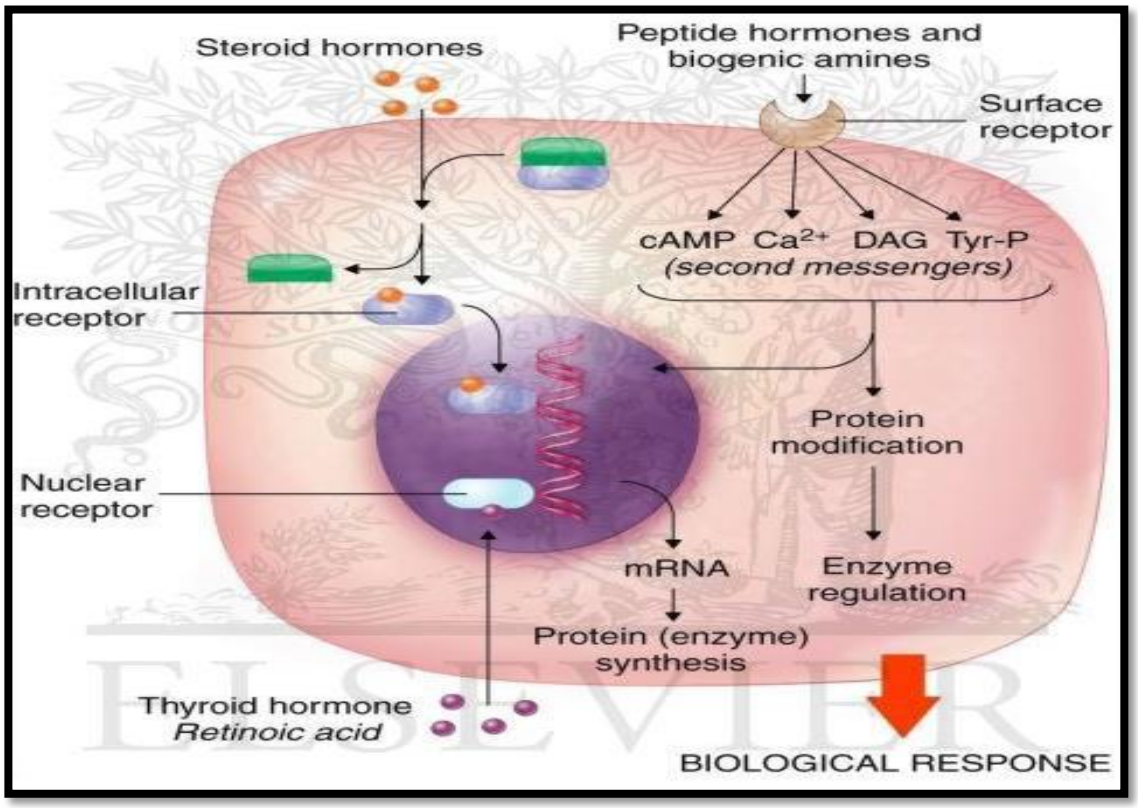

Figure (2) The cell surface and intracellular receptors

Classification of hormones

1. Classification of hormones according to general features of hormone

The hormones can be classified according to their general features, as exhibited in Table (1):

Table (1): Classification of hormones according to general features of hormone

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma half-life	Long (hours to days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, Ca^{2+}, metabolites of complex phosphoinositols, kinase cascades

2. Classification of hormones according to location of receptors (mechanism)

The hormones can also be classified according to location of receptors (mechanism), as exhibited in Table (2):

Table (2) Classification of hormones according to location of receptors (mechanism)

Group I	**Hormones that bind to intracellular receptors**
Androgens, Calcitriol (1,25[OH]2-D3), Estrogens, Glucocorticoids, Mineralocorticoids, Progestins, Retinoic acid and Thyroid hormones (T3 and T4)	
Group II	**Hormones that bind to cell surface receptors**
Group II.A	**The second messenger is cAMP**
α2-Adrenergic catecholamines, β-Adrenergic catecholamines, Adrenocorticotropic hormone (ACTH), Antidiuretic hormone (ADH), Calcitonin, Chorionic gonadotropin (CG), human Corticotropin-releasing hormone (CRH), Follicle-stimulating hormone (FSH), Glucagon, Luteinizing hormone (LH), Melanocyte-stimulating hormone (MSH), Parathyroid hormone (PTH) and Thyroid-stimulating hormone (TSH)	
Group II.B	**The second messenger is cGMP**
Atrial natriuretic factor (ANF)	
Group II.C	**The second messenger is calcium or phosphatidylinositols (or both)**
Acetylcholine (muscarinic), α1-Adrenergic catecholamines, Angiotensin II, Antidiuretic hormone (vasopressin), Cholecystokinin, Gonadotropin-releasing hormone (GRH), Oxytocin and Thyrotropin-releasing hormone (TRH)	
Group II.D	**The second messenger is a kinase or phosphatase cascade**
Erythropoietin, Growth hormone (GH), Insulin, Insulin-like growth factors I and II and Prolactin	

3. Classification of hormones according to chemical diversity of hormones

A. Cholesterol derivative: A large series is derived from cholesterol. These include the glucocorticoids, mineralocorticoids, estrogens, progestins, testosterone and $1,25(OH)_2$-D_3.

B. Amino acid derivative: The amino acid tyrosine is the starting point in the synthesis of the catecholamines and of the thyroid hormones tetraiodothyronine (thyroxine; T4) and triiodothyronine (T3).

C. Peptides of various size: Many hormones are polypeptides. These hormones range in size from thyrotropin-releasing hormone (TRH), a tripeptide, adrenocorticotropic hormone (ACTH; 39 amino acids), parathyroid hormone (PTH; 84 amino acids), and growth hormone (GH; 191 amino acids). Insulin is an AB chain heterodimer of 21 and 30 amino acids, respectively.

D. Glycoproteins: Follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and chorionic gonadotropin (CG) are glycoprotein hormones of α β heterodimeric structure. The **α chain is identical** in all of these hormones, and **distinct β chains** impart hormone uniqueness.

Control of hormone secretion

1. The action of a substance other than a hormone: for example: the influence of blood glucose on insulin secretion from the pancreas. An increasing blood glucose level causes an increase in insulin secretion from the pancreas. Insulin increases glucose movement into cells, resulting in a decrease in blood glucose levels, which in turn causes a decrease in insulin secretion. Thus insulin levels increase and decrease in response to changes in blood glucose levels.

2. Neural control: for example: the neural control of epinephrine and norepinephrine secretion from the adrenal gland. In response to **stimuli** such as stress or exercise, the nervous system stimulates the adrenal gland to secrete epinephrine and norepinephrine,

which help the body respond to the stimuli. When the stimuli are no longer present, secretion of epinephrine and norepinephrine decreases.

3. Feedback: for example: thyroid releasing hormone (TRH) from the hypothalamus in the brain stimulates the secretion of thyroid stimulating hormone (TSH) from the anterior pituitary gland, which, in turn, stimulates the secretion of thyroid hormones from the thyroid gland. A **negative feedback** regulation for regulating thyroid hormone secretion exists because thyroid hormones can inhibit the secretion of TRH and TSH. Thus, the concentrations of TRH, TSH, and thyroid hormone increase and decrease within a normal range.

A few examples of **positive feedback** regulation in the endocrine system exist. Prior to ovulation, estrogen from the ovary stimulates luteinizing hormone (LH) secretion from the anterior pituitary gland. The LH, in turn, stimulates estrogen secretion from the ovary. Consequently, blood levels of estrogen and LH increase prior to ovulation.

4. Inherent rhythms (circadian rhythm): Adrenocorticotrophic hormone (ACTH) is secreted episodically, each pulse being followed 5-10 min later by cortisol secretion. These episodes are most frequent in the early morning (between the fifth and eighth hour of sleep) and least frequent in the few hours before sleep. Plasma cortisol concentrations are usually highest between about 07.00 and 09.00 hour and lowest between 23.00 and 04.00 hour.

Hormone action & signal transduction

Group I hormones interact with an intracellular receptor and group II hormones with receptor recognition sites located on the extracellular surface of the plasma membrane of target cells.

1. Group I hormones

The lipophilic group I hormones diffuse through the plasma membrane of all cells but only encounter their specific, high-affinity intracellular receptors in target cells. These receptors

can be located in the **cytoplasm or in the nucleus** of target cells. The hormone-receptor complex first undergoes an activation reaction. Receptor activation occurs by at least two mechanisms.

For example, **glucocorticoids** diffuse across the plasma membrane and encounter their cognate **receptor in the cytoplasm** of target cells. This step appears to be necessary for subsequent nuclear localization of the glucocorticoid receptor. The now activated receptor moves into the nucleus and binds with high affinity to a specific DNA sequence called the **hormone response element** (HRE). In the case illustrated, this is a **glucocorticoid response element**, or GRE. The DNA-bound, liganded receptor serves as a high-affinity binding site for one or more coactivator proteins, and accelerated gene transcription typically ensues when this occurs.

By contrast, certain hormones such as the thyroid hormones and retinoids diffuse from the extracellular fluid across the plasma membrane and go **directly into the nucleus**. In this case, the cognate receptor is already bound to the HRE (thyroid hormone response element [TRE].

2. Group II hormones

The mechanism of action of this group of hormones can best be discussed in terms of the intracellular signals they generate. These signals include cAMP (cyclic AMP; 3′,5′- cyclic adenosine monophosphate), a nucleotide derived from ATP through the action of adenylyl cyclase; the cGMP, a nucleotide formed by guanylyl cyclase; the Ca^{2+}; and phosphatidylinositides. Many of these **second messengers** affect gene transcription, they also influence a variety of other biologic processes.

Endocrine glands and hormones

The endocrine glands and their hormones are explained in Table (3):

Table (3) The endocrine glands and their hormones

Endocrine Gland and Hormone	Target Tissue	Principal Actions
POSTERIOR LOBE OF PITUITARY		
Antidiuretic hormone (ADH)	Kidneys	Stimulates reabsorption of water; conserves water
Oxytocin	Uterus	Stimulates contraction
	Mammary glands	Stimulates milk ejection
ANTERIOR LOBE OF PITUITARY		
Growth hormone (GH)	Many organs	Stimulates growth by promoting protein synthesis and fat breakdown
Adrenocorticotropic hormone (ACTH)	Adrenal cortex	Stimulates secretion of adrenal cortical hormones such as cortisol
Thyroid-stimulating hormone (TSH)	Thyroid gland	Stimulates thyroxine secretion
Luteinizing hormone (LH)	Gonads	Stimulates ovulation and corpus luteum formation in females; stimulates secretion of testosterone in males
Follicle-stimulating hormone (FSH)	Gonads	Stimulates spermatogenesis in males; stimulates development of ovarian follicles in females
Prolactin (PRL)	Mammary glands	Stimulates milk production
Melanocyte-stimulating hormone (MSH)	Skin	Stimulates color change in reptiles and amphibians; unknown function in mammals
THYROID GLAND		
Thyroxine (thyroid hormone)	Most cells	Stimulates metabolic rate; essential to normal growth and development
Calcitonin	Bone	Lowers blood calcium level by inhibiting loss of calcium from bone
PARATHYROID GLANDS		
Parathyroid hormone	Bone, kidneys, digestive tract	Raises blood calcium level by stimulating bone breakdown; stimulates calcium reabsorption in kidneys; activates vitamin D
ADRENAL MEDULLA		
Epinephrine (adrenaline) and norepinephrine (noradrenaline)	Smooth muscle, cardiac muscle, blood vessels	Initiate stress responses; raise heart rate, blood pressure, metabolic rate; dilate blood vessels; mobilize fat; raise blood glucose level
ADRENAL CORTEX		
Aldosterone	Kidney tubules	Maintains proper balance of Na^+ and K^+ ions
Cortisol	Many organs	Adaptation to long-term stress; raises blood glucose level; mobilizes fat
PANCREAS		
Insulin	Liver, skeletal muscles, adipose tissue	Lowers blood glucose level; stimulates storage of glycogen in liver
Glucagon	Liver, adipose tissue	Raises blood glucose level; stimulates breakdown of glycogen in liver
OVARY		
Estradiol	General	Stimulates development of secondary sex characteristics in females
	Female reproductive structures	Stimulates growth of sex organs at puberty and monthly preparation of uterus for pregnancy
Progesterone	Uterus	Completes preparation for pregnancy
	Mammary glands	Stimulates development
TESTIS		
Testosterone	Many organs	Stimulates development of secondary sex characteristics in males and growth spurt at puberty
	Male reproductive structures	Stimulates development of sex organs; stimulates spermatogenesis

General principles of endocrine diagnosis

Certain hormones, such as growth hormone (secreted from the anterior pituitary gland), thyroxine (secreted from the thyroid gland) and insulin (from the pancreatic islet cells), influence tissue metabolism directly. Conversely, trophic hormones from the pituitary gland stimulate target endocrine glands to synthesize and secrete further hormones, which in turn partly control trophic hormone release, usually by negative feedback inhibition. For example, elevation of plasma T_4 concentration inhibits the secretion of thyroid-stimulating hormone.

Endocrine glands may secrete excessive or deficient amounts of hormone. Abnormalities of target glands may be primary or **secondary to dysfunction of the controlling mechanism, usually located in the hypothalamus or anterior pituitary gland**. Simultaneous measurement of both the trophic hormones and their controlling factors, whether hormones or metabolic products, may be more informative than the measurement of either alone.

If the results be equivocal when considered together with the clinical findings, so-called **'dynamic'** tests should be carried out. In such tests the response of the gland or the feedback mechanism is assessed after stimulation or suppression by the administration of exogenous hormone.

1- Suppression tests are used mainly for the differential diagnosis of excessive hormone secretion. The substance (or an analogue) that normally suppresses secretion by negative feedback is administered and the response is measured. Failure to suppress implies that secretion is not under normal feedback control (autonomous secretion).

2- Stimulation tests are used mainly for the differential diagnosis of deficient hormone secretion. The trophic hormone that normally stimulates secretion is administered and the response is measured. A normal response excludes an abnormality of the target gland, whereas failure to respond confirms it.